REMARKS

Claims 1-27 were canceled previously, without prejudice to the subject matter contained therein. Claims 28-40 are pending. Claims 28-34 have been amended. Support for the new claims exists throughout the specification, for example at pages 26-27, Example 9; Tables 4-8; Figures 7a-7d; and Figures 8a-8d. No new matter is introduced by these amendments.

Rejections under 35 U.S.C. § 112

On pages 2-3 of the Final Office Action mailed October 16, 2007, the Examiner rejects claims 29-40 under 35 U.S.C. § 112, first paragraph, as "failing to comply with the written description requirement." Specifically, the Examiner compares the number of antibodies in the dependent claims with the number of antibodies depicted in the individual embodiments, and rejects the claims because these numbers allegedly do not match. Additionally, the Examiner rejects the claims because she found no support in the figures for "'kappa', lambda, anti-hIg or anti-Ig," although she concedes that Tables 5, 6, and 7 do include anti-hIg. The Examiner concludes that "one of skill in the art would reasonably conclude that the originally filed disclosure fails to support claims 29-40 due to difference in the number of immunoglobulins and the particular immunoglobulins required, such as immunoglobulins to "kappa", "lambda", anti-hIg and anti-Ig versus mIgG1, mIgG2a, mTgG2b, mIgM within the individual disclosed immunoglobulin arrays." Final Office Action, at 3.

Applicants respectfully traverse the rejections. Nevertheless, in an effort to expedite prosecution, the claims have been amended to recite directly the specific embodiments in the corresponding particular Tables and Figures. Hence, there is now clear correspondence between immunoglobulin molecules described in the present application and those recited in the claims. Applicants respectfully request that these § 112, first paragraph, rejections be withdrawn.

Rejections under Rejections under 35 U.S.C. § 103

On pages 3-4 of the Final Office Action, the Examiner rejects claims 28, 29, 35-37, claims 39 and 40 under 35 U.S.C. § 103(a) "as being unpatentable over Diamond et al (WO95/06909) as evidenced by the ATCC attachment in view of Lanza et al … Chang, … and Ruiz-Arguelles et al…." Applicants respectfully traverse the rejection.

The claimed invention is drawn to a method for distinguishing a leukemia of T cell, B cell, or myeloid lineage in a human subject comprising the steps of providing a single assay device including a derivatised solid support having an array of immunoglobulin molecules immobilized in discrete regions on the support, wherein the immunoglobulins are specific for the single cell surface marker antigens CD3, CD4, CD8, CD14, CD19, and CD56, contacting a biological sample containing leukocytes obtained from the human subject with the assay device and allowing the leukocytes in the biological sample to bind to the immunoglobulins on the derivatised solid support via cell surface marker antigens on the leukocytes to form a pattern of binding on the array of discrete regions each being specific for a single cell surface marker presented only once in the array; and determining the relative scale of the pattern of simultaneous binding with which the cell surface marker antigens CD3, CD4, CD8, CD14, CD19, and CD56 on the leukocyte have bound to the immunoglobulins on the array, such that the relative scale of the pattern of CD3, CD4, CD8, CD14, CD19, and CD56 binding on the array distinguishes leukemia of T cell, B cell, or myeloid lineage in the patient.

The claimed invention thus provides a pattern that provides a diagnosis in a single, rapid test, assisting clinicians to achieve a better understanding of their patient's condition and thus provide better treatment. Since the filing of the present patent application, this approach has been applied to the analysis of over 700 patients and has proved over 90% accurate when compared to traditional techniques. Applicant's award-winning technology has been also been commercialized in Australia.

The Examiner alleges that Diamond teaches a method for identifying leukemia lineages via flow cytometry using immunoglobulins to CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11c, CD13, CD14 (My4 and Mo2), CD16, CD19, CD 20, CD 22, CD25, CD33, CD34, CD41, CD45, CD56, CD57, CD61 and CD71 and immunoglobulins that bind to kappa, lambda, GPA (glycophorin A), and HLA-DR. Regarding claim 37, the Examiner asserts that Diamond specifically discloses anti-CD14 antibody "Mo2." Regarding claim 40, the Examiner asserts that Diamond notes that one may further analyze some of the S phase and cell sizes, which correspond to claim 40's recited biochemical analysis. The Examiner concedes that Diamond does not teach a single assay device comprising a solid support having the discreet immunoglobulins arranged in discreet regions. Final Office Action at 4.

Respectfully, the Examiner has oversimplified Diamond, which refers to:

> a system and method for conducting hematopathology diagnosis based on results output from a ***hematology analyzer, flow cytometry*** (FCM) analyzer, ***and review of microscopic slides of bone marrow preparations***. The invention provides a patterned approach to peripheral blood, FCM, and bone marrow analysis and serves to guide technologists and technicians through the complexities of hemogram interpretation, morphologic observations and complementary laboratory studies. Furthermore, the invention guides physicians in the interpretation of FCM studies and provides a means of ***generating multiparameter interpretive reports of hematology specimens. A logical mechanism of diagnostic reasoning is implemented through the use of a computer***.
> Diamond at page 1, lines 11-27 (emphasis added).

In other words, Diamond refers to a complex and detailed analyses required at least three different tests and the building and implementing of a database to which all the test data may be entered before a diagnosis is delivered:

> Thus, in accordance with the invention, the problems of the prior art are avoided by employing a system and method which does not rely upon probability/statistics methodology to arrive at a differential diagnosis or interpretation of test results. Instead, a ***hierarchica***l classification of ***blood, immunophenotype and bone marrow*** patterns is established and a ***heuristic algorithm is applied*** to ***eliminate*** patterns based on data obtained from hematopathology analysis. For purposes of this disclosure, by "differential diagnosis" is meant a list of possible diagnoses or diagnostic possibilities. Further, by "interpretation of test results" is meant a diagnostic impression based on available data. Page 5, lines 9-23 (emphasis added).

> In its present implementation, the system in accordance of the invention consists of ***three knowledge based modules***, i.e., a ***hematology*** module 12a, a ***flow cytometry*** module 12b and a ***bone marrow*** module 12c, ***along with associated databases*** 14, an electronic textbook 16 with digitized images of, for example, abnormal blood cells, and in addition, educational materials... Page 33, lines 7-14 (emphasis added).

According to Diamond, an example diagnosis of acute myeloid leukemia would involve these and other tests:

> In FIG. 12 there is illustrated the final interpretation and recommendation screen of the hematology blood module 12 a, known as "Professor Petrushka." the highest pattern matched in the hierarchy "abnormal mononuclear cell pattern" is displayed in a scrollable field along with 1) the specific findings in the peripheral blood; 2) the

differential diagnosis (which, in this case consists of only one diagnosis); and 3) a statement as to the specific diagnosis "acute myeloid leukemia" suggested by the finding "auer rods present." The recommendations for follow-up tests in this case are shown as including a bone marrow aspirate/biopsy, cytochemical stains, and immunophenotyping by flow cytometry. Page 31, lines 11-25.

The flow cytometry input parameters of Diamond are shown as follows:

TABLE V

FLOW CYTOMETRY INPUT PARAMETERS

1.	Age	24.	CD45
2.	Sex	25.	CD56
3.	Specimen Type	26.	CD57
4.	CD1a	27.	CD61

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5.	CD2	28.	CD71
6.	CD3	29.	Kappa
7.	CD4	30.	Lambda
8.	CD5	31.	Ia (HLA-DR)
9.	CD7	32.	Glycophorin A
10.	CD8	33.	Cytoplasmic Kappa
11.	CD10	34.	Cytoplasmic Lambda
12.	CD11c	35.	Cytoplasmic Mu
13.	CD13	36.	Cytoplasmic CD3
14.	MY4 (CD14)	37.	Cytoplasmic CD22
15.	Mo2 (CD14)	38.	Tdt
16.	CD16	39.	Myeloperoxidase (by cytochemistry)
17.	CD19	40.	Myeloperoxidase (by monoclonal antibody)
18.	CD20	41.	Cell Size [Small, Medium, Large, Variable, Bimodal]
19.	CD22	42.	DNA-Index
20.	CD25	43.	% S-phase
21.	CD33	44.	% Abnormal Cells
22.	CD34	45.	% Blasts or Promyelocytes Present
23.	CD41	46.	Peripheral blood and clinical findings [from database 34]

For Item 3, Specimen Types are: PB=Peripheral Blood, BM=Bone Marrow, LN=Lymph Node, SP=Spleen, PL=Fluid, EN=Extranodal

Items 4-40 are expressed either: (1) as percent positive (>30=positive); or, (2) by fluorescence intensity [-/+/++/+++] (except item 39)

During Data Abstraction (Step 56) Items 4-40 are designated: POSITIVE (%>30 or + or ++ or +++), NEGATIVE (%<=30 or -) or NOT DONE.

There are over thirty markers which would be tested in the method of Diamond. Using flow cytometry, as taught by Diamond in the early 1990's, in which only two or three antibodies could be run in a single assay, would take days to complete. This panel would then be compared with other data in the database before a diagnosis might be derived.

This is a far cry from the instant claimed method, in with a single assay comprising CD3, CD4, CD8, CD14, CD19, and CD56 allows for an accurate determination. That these six markers are included in a list of over thirty markers that are analyzed with hosts of other data, is no more than a mere coincidence in the context of Diamond, which nowhere teaches or suggests that the pattern of binding of these markers alone, with no further testing, can determine leukemia lineage. The 'patterns' to which Diamond refers relate to generating ***multiparameter*** interpretive reports and a logical mechanism of diagnostic reasoning implemented through the use of a computer. This is not the pattern of simultaneous binding of CD3, CD4, CD8, CD14, CD19, and CD56 in a single assay.

Regarding Lanza, the Examiner maintains that Lanza discloses a method for determining leukemia lineages via flow cytometry using MAbs to CD64, CD117, CD13, CD33, CD14, CD15, CD61, CD41, and glycophorin A to identify myeloid lineage leukemia cell; MAbs to CD2, CD3, CD4, CD5, CD7, and CD8 to identify T lymphoid leukemia cells; MAbs to CD79α, CD10, CD19, CD20, CD22, CD24, kappa and lambda to identify B-lymphoid leukemia cells in addition to CD9, CD11b CD11c, CD25, CD34, CD38, CD45RO, CD45RA, CD56, CD71, and HLA-DR. The Examiner notes that Lanza admits a that flow cytometry may yield false positive or false negative results depending on the threshold for positivity. The Examiner concedes that Lanza does not teach the use of an antibody array comprising the antibodies used in the flow cytometric determination. Final Office Action at 4.

If one were to follow the teachings of Lanza, it would take days to complete flow cytometric analyses of all of these markers. Importantly, Lanza does not provide any indication that the six markers of claim 28 (CD3, CD4, CD8, CD14, CD19, and CD56), as opposed to any of Lanza's other thirty-two antibodies listed by the Examiner, provide as a consensus marker panel to distinguish between T cell, B cell, or myeloid lineage leukemias. Indeed, Lanza notes that "***There is a need to standardize the panel*** of McAbs to be used for the characterization and classification of acute leukemias," and "it must be said that the panel of markers is only

provisional, since the number of useful reagents is growing rapidly, and therefore **it is wise to wait** the conclusion of some ongoing studies **before** including some of these recently developed antibodies into a new proposed list of McAbs." Lanza, page 10, first column.

Clearly Lanza recognizes the need answered by the claimed invention: for a standardized panel. According to the claimed method, the binding pattern of CD3, CD4, CD8, CD14, CD19, and CD56 provides this panel and distinguishes leukemia of T cell, B cell, or myeloid lineage in a patient.

In re O'Farrell, is instructive on the present rejection:

> The admonition that "obvious to try" is not the standard has been directed mainly at two kinds of error. In some cases, ***what would have been "obvious to try" would have been to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many choices were likely to be successful.*** … In others what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave ***only general guidance*** as to the ***particular form*** of the claimed invention or how to achieve it. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988) (emphasis added).

There are almost 200 possible combinations of antibodies listed by the Examiner for each indication, with no direction to arrive at the panel of CD3, CD4, CD8, CD14, CD19, and CD56 that can in a single, simultaneous assay distinguish T cell, B cell, or myeloid lineage leukemia. The Examiner notes that Lanza does not teach the use of an antibody array, but that is an understatement: Lanza is utterly silent regarding any solid-support based assay system and does not even hint at a single assay device having an array of immunoglobulin molecules immobilized in discrete regions on the solid support. Moreover, nothing in Lanza suggests employing the panel of six cell surface marker antigens (as in claim 28) with the contacted leukocytes to form a simultaneous pattern of binding of CD3, CD4, CD8, CD14, CD19, and CD56 on the single array, and then determining the relative scale of the pattern of binding of such that the relative pattern of binding on the array distinguishes leukemia of T cell, B cell, or myeloid lineage in a patient.

Regarding Ruiz-Arguelles, the Examiner maintains that Ruiz-Argulles teaches the flow cytometric immunophenotyping of leukemia cells and that "the relative intensity of a given antigen can be different from normal and thus classified as dim or bright relative to normal." Final Office Action at 4.

The Examiner completely ignores that Ruiz-Arguelles cites and flatly ***contradicts*** Lanza, and teaches away from the claimed invention. More specifically, comparing Lanza's Table IV with Ruiz-Arguelles Tables 1 and 2, the Examiner should note the inconsistencies: certain antibodies are present while others are absent and yet others are designated as markers for inapposite diagnoses. It is improper for the Examiner to pick some aspects of some art and ignore what is said in other art. The MPEP, at § 2141, instructs that "references must be considered ***as a whole*** and ***must suggest the desirability*** and thus the obviousness ***of making the combination***; … references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and … reasonable expectation of success is the standard with which obviousness is determined."

For ease in comparison, Lanza table IV, from page 11, is recreated below:

Table IV Proposed panel of monoclonal antibodies to be used for the characterization of acute leukemia cells	
Myeloid	1st level: anti-MPO, CD64, CD117, CD13, CD33, CDw65 2nd level: anti-lysozyme, CD14, CD15, CD61, CD41, glicophorin A (uPA-R-CD87), (GM-CSF-R-CDw116)
T-Lymphoid	1st level: cyCD3, anti-TCR α/β (TCR β chain), CD2, CD7 2nd level: CD1, CD4, CD8, CD5, TCRγ/δ
B-lymphoid	1st level: CD79α, cyCD22, CD19, CD10 2nd level: CD20, CD24, cμ, clg (κ, γ, M,D,G,A)
Non-lineage specific	CD23, HLA-DR, CD38, CD71, Thy-1 (CD90), CD45RO, CD45RA, TdT
Miscellaneous	CD56, CD9, CD35, CD11b, CD11c, CD25
In parenthesis it has been shown that McAbs whose reactivity and specificity has to be confirmed in larger series of patients.	

Ruiz-Arguelles Tables 1 and 2, from page 41are recreated below:

Table 1
Antibodies to Define Lineage and Degree of Immaturity in Acute Lukemia[a]

Purpose	B-ALL	T-ALL	AML
Lineage definition	CD79α/CD19	CD3c/CD7	MPOc/CD13, 33
Maturation	cd34/TdT	CD34/TdT	CD34/CD15/HLADR

[a]B-ALL, B-cell acute lymphoblastic leukemia; TALL, T-cell acute lymphoblastic leukemia; AML, acture myeloid leukemia; CD3c, cytoplasmic CD3; MPOc, cytoplasmic myeloperoxidase; TdT, terminal deoxynucleotidyl transferase.

Table 2
Antibodies to Define Lineage and Classify Lymphoproliferative syndromes[b]

Purpose	B-LPS	T-LPS	NK-LPS
Lineage definition	CD20/κ/λ	CD3	CD3/CD16/CD56
Classification	CD5/CD22/CD23 CD11c/CD19/FMC7 CD25/CD103	CD4/CD8 αβ/γδ	CD2/CD5/CD8

[b]B-LPS, B-cell lymphoproliferation syndrome; T-LPS, T-cell lymphoproliferation syndrome; NK-LPS, NK-cell lymphoproliferation syndrome.

Hence, one skilled in the art would not, and could not, simply combine Lanza and Ruiz-Arguelles to define the CD3, CD4, CD8, CD14, CD19, and CD56 markers of the claimed method that, in a single, simultaneous assay, distinguishes leukemia of T cell, B cell, or myeloid lineage in a patient. Indeed, one of the claimed markers, CD14, is absent from Ruiz-Arguelles. In the context of the *In re O'Farrell* case, there is no indication of which of the numerous choices would lead to the claimed, successful six markers that distinguish the leukemia lineage. There are certainly several antibodies included in the pending dependent claims that are not mentioned at all in Ruiz-Arguelles.

Indeed, regarding diagnoses, Ruiz-Arguelles instructs that "in the case where the ***diagnosis*** of acute leukemia is made from clinical and morphological data, ***this minimum panel of 14 antibodies*** will provide the ***necessary*** information for determining lineage and maturity." Ruiz-Arguelles clearly teaches away from the six consensus markers, CD3, CD4, CD8, CD14,

CD19, and CD56, of the claimed method. The Examiner can not simply ignore this teaching. A prima facie case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997)

The Examiner's note that that Ruiz-Arguelles classifications of "dim or bright" or "different from normal" hardly suggests a single assay device comprising a derivatised solid support with immunoglobulins for CD3, CD4, CD8, CD14, CD19, and CD56 markers with which leukocytes may bind such that the relative scale of the simultaneous pattern of binding of CD3, CD4, CD8, CD14, CD19, and CD56 markers on the array distinguishes leukemia of T cell, B cell, or myeloid lineage.

The Examiner maintains that Chang teaches the binding of cells to matrixes of distinct antibodies coated on solid surfaces, and that such as matrix can be used to analyze functionality of different cell subpopulations.

According to the Examiner, Chang suggests that the array can be read with a microscope as recited in claim 36. Chang also allegedly teaches an embodiment in which no fluorescent staining was included, and allegedly allows for exposure of a sample to all antibodies at discrete location at the same time. Final Office Action at 5.

Chang notes that "**if** antibodies of relevant but distinct specificities can be prepared and purified, they can be coated on a small area of a surface and be used to analyze antigens." Yet Chang used only two antibodies and three types of cells. In each instance, the antibody and cell were known to interact before the experiment, thus Chang did not provide any test of wherein a cell sample of unknown character was identified by an antibody. Chang's statement that "It is apparent that the analysis of the cell binding results would be facilitated with proper instruments," hardly provides assistance, given that such instruments were not in existence (Chang evaluated binding via "naked eye," see page 219, second full paragraph). Chang certainly does not provide for the six consensus immunoglobulins for CD3, CD4, CD8, CD14, CD19, and CD56, of claim 28, as a consensus marker panel to distinguish between T cell, B cell, or myeloid lineage leukemias. Indeed, Chang is completely silent regarding leukemia, and never mentions

the application of the technique to any diagnostic screening or in particular to characterizing leukemias, and hence would not suggest combination with Lanza and/or Ruiz-Arguelles..

Moreover, the Declaration of Richard Ian Christopherson dated 28 September 2004, of record, states that the glass coverslips of Chang could not be used to effect the methods of the claimed invention because, *inter alia*, antibodies do not adhere reliably to plain glass slides, and because leukocytes bind to the glass itself causing high background. Christopherson Declaration at paragraphs 5 and 6. Indeed, the claimed method uses a derivatised solid support, thus avoiding these problems. Such derivatisation is explained in the specification at, for example, at the paragraph bridging pages 26 and 27 ([0122] of the published version), which states:

> The solid support is typically glass or a polymer, such as but not limited to cellulose, ceramic material, nitrocellulose, polyacrylamide, nylon, polystyrene and its derivatives, polyvinylidene difluoride (PVDF), methacrylate and its derivatives, polyvinyl chloride or polypropylene. … A solid support may also be a hybrid such as a nitrocellulose film supported on a glass or polymer matrix. Reference to a "hybrid" includes reference to a layered arrangement of two or more glass or polymer surfaces listed above. The solid support may be in the form of a membrane or tubes, beads, discs or microplates, or any other surface suitable for conducting an assay. Binding processes to immobilize the molecules are well-known in the art and generally consist of covalently binding (e.g. cross linking) or physically adsorbing the molecules to the solid substrate.

Dr. Christopherson, at paragraph 5 of his Declaration, refers to such treated supports as derivatised rather than hybrid, but the meaning is clear to one of ordinary skill. Chang does not suggest derivatisation of the surface of the solid support, indeed because that technology was not available. *Id.*

Importantly, Chang states that, "it is possible that the matrix method can be used to determine the proportion of specific subsets in a mixed population, e.g., the proportions of B cells, T cells, and monocytes in the mononuclear cell fraction or the proportions of inducer and suppressor T cell in the T cell fraction." Chang, at page 223. Thus, Chang refers only to identification of ***cell types***, and not to the complex patterns of expression of markers that are associated with leukemia diseases. As Dr. Christopherson explained in paragraph 5 of the Declaration:

> The differential pattern of interaction indicates the relative density of interaction between each immunoglobulin and its cognate cell surface antigen, which may result, for example, from ***differential density*** of cells that bind to a discrete spot on the array, the ***differential expression*** of particular antigens, and/or the ***number of antigens*** per cell.

The Examiner states, on page 5 of the Final Office Action, that "one of skill in the art would have been motivated to dilute the sample such that not all of the antibody dots were filled to capacity as indicated by Chang. By doing so it would allow for the relative assessment of cell binding relative to a normal cell sample and thus replace the classification of dim or bright as assess by flow cytometry of Ruiz-Arguelles. … this would allow for comparison to the normal sample to be made which would reflect actually relative differences between antigen expression in a patient sample and a normal sample which can then be construed…" This statement indicates the clear distinctions between the claimed invention and the cited art:

According to the claimed method, the array has discrete regions each being specific for a single cell surface marker presented only once in the array: there is no diluting step involved in generating the claimed pattern;

The simultaneous expression pattern of CD3, CD4, CD8, CD14, CD19, and CD56 relates only to the leukocytes collected from one subject, there is no "normal cell sample" associated with the claimed method.

The *In re O'Farrell* case noted above is particularly instructive to the instant rejection. The Diamond, Lanza, and Ruiz-Arguelles cases suggest scores of parameters and numerous possible choices and no indication of which parameters are critical, and Chang, at best, provides only general guidance in a promising field of experimentation. The combination of these references simply do not suggest or provide for any expectation that the simultaneous pattern of discrete regions each being specific for a single cell surface marker presented only once such that the relative scale of simultaneous binding pattern of CD3, CD4, CD8, CD14, CD19, and CD56 markers would provide for a single assay capable of distinguishing between leukemia of T cell, B cell, or myeloid lineage in the subject.

Hence, because this § 103 rejection is inadequately supported by the cited references, Applicants respectfully request that it be withdrawn.

The Examiner, on page 6 of the Final Office Action, maintains the rejection of claims 28, 29, and 35-40 under 35 U.S.C. § 103(a) "as being unpatentable over Diamond et al, Lanza et al, Chang and Ruiz-Arguelles et al … and further in view of Shyjan (U.S. 5,674,739)." The Examiner states that Shyjan teaches the use of polyclonal antibodies where the target is mutated, and concludes that it would have been obvious to use polyclonal antibodies against the antigens taught be Diamond and Lanza to "insure that the targeted antigen will still bind to the immunoglobulin in instances where the targeted antigen is mutated." Final Office Action at page 6. Applicants respectfully traverse the rejection.

The Examiner states that "Shyjan teaches the use of polyclonal antibodies in instances where the target is mutated (column 25, lines 17-21)," and in doing so refers to one term in Shyjan with complete disregard for its context. Shyjan recites, at column 25, lines 6-24:

> Additionally, an expression library can be constructed utilizing DNA isolated from or cDNA synthesized from a tissue known to or suspected of expressing the gene of interest in an individual suspected of or known to carry the mutant allele. In this manner, gene products made by the putatively mutant tissue can be expressed and screened using standard antibody screening techniques in conjunction with antibodies raised against the normal gene product, as described, below, in Section 5.2.3. (For screening techniques, see, for example, Harlow, E. and Lane, eds., 1988, "Antibodies A Laboratory Manual," Cold Spring Harbor Press, Cold Spring Harbor.) In cases where the mutation results in an expressed gene product with altered function (e.g., as a result of a missense mutation), a polyclonal set of antibodies are likely to cross-react with the mutant gene product. Library clones detected via their reaction with such labeled antibodies can be purified and subjected to sequence analysis as described in this Section, above.

Clearly, Shyjan has nothing whatsoever to do with the claimed invention, which provides for a method for distinguishing a leukemia of T cell, B cell, or myeloid lineage in a human subject comprising the steps of providing a single assay device including a derivatised solid support slide having an array of immunoglobulin molecules immobilized in discrete regions on the support, wherein the immunoglobulins are specific for the single cell surface marker antigens CD3, CD4, CD8, CD14, CD19, and CD56; contacting a biological sample containing leukocytes obtained from the human subject with the assay device and allowing the leukocytes in the biological sample to bind to the immunoglobulins on the derivatised solid support via cell surface marker antigens on the leukocytes to form a pattern of binding on the array of discrete regions each being specific for a single cell surface marker presented only once in the array; and

determining the relative scale of the pattern of simultaneous binding with which the cell surface marker antigens CD3, CD4, CD8, CD14, CD19, and CD56 on the leukocyte have bound to the immunoglobulins on the array, such that the relative scale of the pattern of CD3, CD4, CD8, CD14, CD19, and CD56 binding on the array distinguishes leukemia of T cell, B cell, or myeloid lineage in the patient.

Moreover, the Court has instructed that objective evidence relevant to the issue of obviousness, i.e., secondary factors, ***must*** be evaluated by Office personnel. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Such evidence may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. The Applicants have presented such evidence in the last Amendment, but this has not been acknowledged by the Examiner. For example, Chang published in 1983, and supports a finding of long-felt need for the instant approach using an array on commercial scale. Lanza stated, in 1996, that "There is a need to standardize the panel of McAbs to be used for the characterization and classification of acute leukemias," clearly reflecting unsolved needs and the failure of others. This is further evidenced by the statements in Ruiz-Arguelles that contradict Lanza.

Applicants previously invited the Examiner's attention to the MEDSAIC press release, which reports that Applicants' licensee received the 2005 "BioFirst Commercialisation Award" for outstanding achievement in technology for its leukemia and lymphoma diagnostic. In addition to the recognition of commercial development and success in Australia, MEDSAIC was deemed most likely to achieve international success with its technology. This award evidences the recognition of others and commercial success of the claimed invention.

Applicants also provided the Examiner a recent, pier-reviewed article validating the Applicants application of the instant technology: Belov et al., "Analysis of Human Leukemias and Lymphomas Using Extensive Immunophenotypes from an Antibody Microarray," 135 British Journal of Haematology, 134-97 (2006). In this article, the claimed invention provided for a single assay device in which 82 markers could be studied simultaneously. Over 700 patients were profiled and the levels of consensus for classification using standard criteria were more than 90% accurate. This paper clearly evidences the improvement over any of the techniques addressed in the art cited by the Examiner. In summary, comparing all of the cited references, in combination, to the claimed invention, it is clear that claimed invention reflects an advancement

and "real innovation." *KSR Int'l. Co v. Teleflex Inc.*, No. 04-1350 (April 30, 2007) at 15. Hence, Applicants request that the § 103 rejections be withdrawn.

CONCLUSION

Applicants respectfully request reconsideration of this application and allowance of the pending claims in view of the above remarks.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

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